REMARKS

Status of the Claims

Claims 12-22 and 27-32 are in the application.

Claims 12-22 and 27-32 were rejected.

Claims 22 has been amended and new claims 33-38 has been added.

Upon entry of this amendment, claims 12-22 and 27-38 will be pending.

Summary of the Amendment

Claim 22 has been amended to correct the preamble in order to be consistent with that of claim 12 on which claim 22 depends.

New claim 33 relates to specific embodiments which combine the limitations of claims 12, 13 and 18. That is the method of new claim 33 refers to making a microRNA by selecting a target mRNA, generating a microRNA oligonucleotide sequence having specific structural features includes a degree of complementarity to the target mRNA sequence, determining the free energy of a microRNA that has the microRNA oligonucleotide sequence bound to the target mRNA sequence and synthesizing an mRNA having the microRNA oligonucleotide sequence. Support for new claim 33 is found throughout the specification and claims as filed.

New claims 34-38 correspond to claims 14, 15, 17, 27 and 28. Support for new claims 34-38 is found throughout the specification and claims as filed.

No new matter has been added.

Claim Rejections - 35 U.S.C. §103

Claims 12-22, 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over McManus et al (RNA, Vol. 8, pages 842-850 (2002)), Chen et al (US 2005/0008617) and Vargeese et al (US 2004/0249178), the combination in view of Bentwich (USPN 7,696,342).

McManus et al (RNA, Vol. 8, pages 842-850 (2002)) is asserted to teach the design and testing of microRNA which are directed to a preselected target mRNA sequence. The Office asserts the entire document discloses the asserted subject matter especially the text in the

Results and Discussion section on pages 843-848 and Fig. 1; p. 843, Fig. 2, p. 844; Fig. 3, p. 845; Fig. 4, p. 846; Fig. 6, p. 848.

Chen et al (US 2005/0008617) is asserted to teach the design and assessment of iRNA molecules, including siRNA and shRNA molecules, for targeting and inhibiting mRNA expression. The Office refers to Fig. 3, 4, 6, 7b, pages 1, 6-8, 11-13, 19-21 of Chen et al as being especially relevant. Chen is also asserted to teach determining free energy for the bound iRNA to a selected mRNA target sequence as a means of determining the binding affinity between the iRNA and its target sequence (see esp. paragraph 0086).

Vargeese et al (US 2004/0249178) is asserted to teach the structures and inhibitory activities of various short interfering nucleic acids, including siRNA, dsRNA, and micro-RNA, and their design and use for inhibiting the expression of a target gene of known sequence. The Office indicates that paragraphs 0416, 0577, 0578 are of particular interest in this regard..

Bentwich (US 7,696,342) is asserted to teach the use of computer systems, including bioinformatic gene detection engines, for collecting data obtained from detecting and analyzing micro RNA (miRNA) genes, as well as their respective target binding sites, and comparing miRNA molecules with their target gene binding sites, and monitoring the miRNA's ability to inhibit target gene expression. The Office indicates that Figures 1 -3 and the text describing those figures are of special interest.

As noted in the Official Action, the primary references do not teach computer systems or programs for identifying microRNA-recognition elements.

It is asserted that it would have been obvious to one skilled in the art to generate microRNA comprising the steps instantly claimed because McManus generated microRNA utilizing most of the steps claimed, in producing microRNA which provides efficient and effective target gene inhibition, which microRNA comprise essentially all of the characteristics as instantly claimed. It is asserted that McManus provides a comparison of microRNA activity as a function of the positions and frequency of mismatches, loops and bulges. Moreover, it is asserted that Chen teaches the design and testing of microRNA molecules, as well as siRNA molecules, which molecules are tested as a function of inserted mismatches in the various

sections of the dsRNA molecules as instantly claimed, as well as loops and bulges. The Office states that the art therefore discloses the routine experimentation involved in designing the microRNA molecules as instantly claimed, and testing them for their ability to inhibit target gene expression. It is asserted that one skilled in the art would have had a reasonable expectation of success that microRNA molecules with the characteristics claimed would provide for effective target gene inhibition and that it was routine in the art to design and test microRNA molecules of the lengths as instantly claimed, before and after inserting bulges, mismatches and loops in the various segments of the molecule, and compare them to other siNAs for target gene inhibition, relying on the combined teachings of McManus, Chen and Vargeese.

It is asserted that one would have been motivated to use computer systems and programs for analyzing the data accumulated in testing the design of microRNA, comparing optimal design choices with the target sequences of the target genes, because this computer capability was well known in the art, and used routinely in determining the relationship between target gene sequences and microRNA molecules, as taught previously by Bentwich. The computer software was readily accessible, and used to routinely to acquire larger amounts of bioinformatic data than single assays would provide.

Thus, it is asserted that the invention would have been obvious to one of skill in the art at the time of filing. Applicants respectfully disagree.

Neither McManus, Chen or Vargeese teach or suggest generating microRNA oligonucleotide sequences against target mRNA sequences as set forth in claim 12.

McManus discloses hairpin RNA molecules. As noted in McManus, the class I hairpins are based upon siRNA structures which are essentially covalently linked to form hairpins. The structure of these hairpins is unrelated to the claimed invention. The claims II hairpins disclosed in McManus are indicated by the authors to be "reminiscent" of a microRNA precursor structure. The synthetic hairpins do not contain the structural features set forth in the claims. As noted in McManus, a GC clamp is provided at the end of the stem portion of the hairpin. This sequence is provided without regard to the sequence of the mRNA target

sequence but rather to complementarity within the hairpin structure only. Nothing in McManus teaches or suggests methods of making microRNAs against specific mRNA target sequences.

Chen dislcoses to siRNA, not microRNA, a related but distinct RNAi based gene silencing phenomenon. The RNAi compositions disclosed in Chen are all based upon siRNA and there is no disclosure of structures unrelated to the claimed invention. Nothing in Chen teaches or suggests methods of making microRNAs against specific mRNA target sequences.

Vargeese dislcoses to conjugates for delivering various active RNA species generally but contains no disclosure regarding the specific structures of the molecules. Nothing in Vargeese teaches or suggests the claimed invention. Nothing in Vargeese teaches or suggests methods of making microRNAs against specific mRNA target sequences.

Bentwich discloses the use of computer systems in bioinformatics applications. However, as noted above none of McManus, Chen or Vargeese teach or suggest the methods of generating or preparing microRNA according to the claimed invention. Bentwich provides no disclosure to overcome this deficit. While Bentwich suggests the use of computer technology in processing biologicial sequence data, Bentwich provides no teachings related to microRNA missing from McManus, Chen and Vargeese. The combination of McManus, Chen, Vargeese and Bentwich do not yield the present invention.

The Official Action states that McManus teaches mRNA target specific microRNAs which

> comprise 17-25 nucleotides, and which comprises a 5' proximal region between 7-9 nucleobases, which is optionally completely complementary to the target mRNA, has a single mismatch in the proximal region, which further comprises a loop region that is 3' to the proximal region, and which is optionally between 0-9 nucleobases and optionally comprises 2-5 non-paired sequences with the target mRNA, and which further comprises a distal region which is 3' to the loop region, and optionally comprises 7 contiguous complementary sequences at the 5' end of the distal region, or comprises 1-4 contiguous mismatches and has complementarity with 5 nucleobases on the distal region, including the 5' end of the distal region

First, McManus does not teach microRNA molecules. Rather, McManus discloses hairpin molecules which do not have physical structures corresponding to microRNAs as set forth in the claims. Contrary to the Office Action McManus does not disclose microRNAs having the structures set forth in the claims including sequences with complementarity to the target mRNA as set forth in the claims. Applicants respectfully urge that the Office is mistaken in the factual assertions in the Office Action. Applicants respectfully urge that McManus does not teach one skilled in the art the structure and nature of microRNA complementarity to target mRNA sequences.

Similarly, Chen is erroneously asserted to disclose information which is not present in its disclosure. Contrary to the assertions in the Official Action, Chen does not disclose RNAi molecules, comprising 17-25 nucleotides including a

> 5' proximal region between 7-9 nucleobases, which is optionally completely complementary to the target mRNA, has a single mismatch in the proximal region, which further comprises a loop region that is 3' to the proximal region, and which is optionally between 0-9 nucleobases and optionally comprises 2-5 non-paired sequences with the target mRNA, and which further comprises a distal region which is 3' to the loop region, and optionally comprises 7 contiguous complementary sequences at the 5' end of the distal region, or comprises 1-4 contiguous mismatches and has complementarity with 5 nucleobases on the distal region, including the 5' end of the distal region, or have a mismatch symmetrically placed between the 5' and 3' end of the proximal region.

The instant claims to methods, systems and computer programs is neither disclosed in Chen nor suggested in any respect. applicant respectfully urges that the reliance on Chen is misplaced and without merit.

Likewise, Valgeese does not disclose or suggest the specific details which are elements of the instant claims. Nothing in Valgeese suggests methods of generating and preparing the microRNA structures as set forth in the claims.

Applicant respectfully urges that none of McManus, Chen and Valgeese teach or suggest the methods of the claimed invention, nor do they provide one skilled in the art information which can be combined together and with Bentwich to yield the present invention.

The combination of McManus, Chen. Valgeese and Bentwich do not produce the claimed invention. The rejection does not establish a prima facie case of obviousness. Claims 12-22, 27-32 are not obvious over McManus et al (RNA, Vol. 8, pages 842-850 (2002)), Chen et al (US 2005/0008617) and Vargeese et al (US 2004/0249178), in view of Bentwich (USPN 7,696,342). Applicant respectfully requests that the rejection of claims 12-22, 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over McManus et al (RNA, Vol. 8, pages 842-850 (2002)), Chen et al (US 2005/0008617) and Vargeese et al (US 2004/0249178), the combination in view of Bentwich (USPN 7,696,342) be withdrawn..

Conclusion

Claims 12-17, 19-22 and 27-38 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 610.640.7855 to clarify any unresolved issues raised by this response.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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